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FO	RMPT	0-1390	(Modified) U.S. DEPARTMENT	OF COMMERCEPATENTAND TRADEMARKOFFICE	ATTORNEY SDOCKETNUMBER
(RI	EV 11-	2000) TR	ANSMITTAL LETTER	TO THE UNITED STATES	PU3556USW
			DESIGNATED/ELECTE		U.S. APPLICATIONNO. (IF KNOWN, SEE 37 CFR
				G UNDER 35 U.S.C. 371	1 09/830037
			ONCERNING A FILIN	INTERNATIONALFILINGDATE	PRIORITYDATECLAIMED
IIN	HER		CT/GB99/03472	20 October 1999	22 October 1998
			IVENTION	IMPROVED VASOCONSTRICTOR	ACTIVITY
1	FLU	TIC	ASONE LOTION HAVING	, IMPROVED VASOCONSTRICTOR	ACTIVITY
			WOMEN DO TO THE		
A	Gor	:don	T(S)FOR DO/EO/US J. DOW: Keith Arthur JOH	NSON; Frances Furr KELLY; Robert	William LATHROP;
			RAJAGOPALAN		
Α	pplic	ant h	erewith submits to the United Sta	tes Designated/Elected Office (DO/EO/US) the	he following items and other information:
1	1.	×		tems concerning a filing under 35 U S.C. 371	
1	2.	П		UENT submission of items concerning a filit	
	3.	×	This is an express request to beg	in national examination procedures (35 U S.C	371(f)). The sybmission must include itens (5),
l		_	(6), (9) and (24) indicated below	expiration of 19 months from the priority date	e (Article 31)
l	4.				(Milele 31)
ı	5.	Δ	A copy of the International Application as filed (35 U S C. 371 (c) (2)) a. is attached hereto (required only if not communicated by the International Bureau)		
ı				by the International Bureau.	
١				application was filed in the United States Reco	eiving Office (RO/US).
ı	6.			of the International Application as filed (35)	
١	0.		a. is attached hereto.		
ı				bmitted under 35 U.S.C. 154(d)(4).	
ı	7.	X		e International Application under PCT Article	e 19 (35 U.S.C 371 (c)(3))
ı				quired only if not communicated by the Inter-	
ı				ted by the International Bureau.	
ı				owever, the time limit for making such amen-	dments has NOT expired
١			d. Maye not been made ar	nd will not be made	
l	8.		An English language translation	of the amendments to the claims under PCT	Article 19 (35 U.S.C. 371(c)(3)).
۱	9.	\boxtimes		ventor(s) (35 U.S.C. 371 (c)(4)).	
١	10.		An English language translation Art « le 35 (35 U.S.C 371 (c)(5)	of the annexes of the International Prelimina	ry Examination Report under PCT
ı	11.	\boxtimes	A copy of the International Prel	iminary Examination Report (PCT/IPEA/409))
۱	12.	\times	A copy of the International Sea	rch Report (PCT/ISA/210).	
۱	I	tems	13 to 20 below concern documen	nt(s) or information included:	
١	13.	\boxtimes		tement under 37 CFR 1 97 and I 98.	
ı	14.		An assignment document for re	ecording A separate cover sheet in compliance	e with 37 CFR 3.28 and 3 31 is included
۱	15.	X	A FIRST preliminary amendment	ent	
1	16		A SECOND OF SUBSECUENT	F preliminary amendment	

- 17.

 A substitute specification.
- 18.

 A change of power of attorney and/or address letter.
- 19.

 A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1821 1.825.
- 20.

 A second copy of the published international application under 35 U.S.C. 154(d)(4).
- 21.

 A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
- 22.

 Certificate of Mailing by Express Mail
- 23. S Other items or information

Copy of PCT Request (Form PCT/RO/101)

Copy of PCT Publication cover

Copy 61 Correction to PCT Request before 30th Month

JC02 Rec'd PCT/PTO 2 n APR 2001 ATTORNEY'S DOCKETNUMBER U.S. APPLICATIONNO, (IF KNOWN, SEE 37 CFR INTERNATIONALAPPLICATIONNO. `ጸ 30 0 PCT/GR99/03472 PH3556USW CALCULATIONS PTOUSEONLY 24. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00 \$860.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1 445(a)(2)) paid to USPTO \$710.00 ☐ International preliminary examination fee (37 CFR 1 482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) . \$690.00 ☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT = \$860.00 Surcharge of \$130.00 for furnishing the oath or declaration later than \$0.00 months from the earliest claimed priority date (37 CFR 1.492 (e)) NUMBER EXTRA RATE NUMBER FILED \$18.00 \$72.00 4 Total claims \$80.00 \$80,00 - 3 = Independent claims 4 \$0.00 Multiple Dependent Claims (check if applicable) TOTAL OF ABOVE CALCULATIONS \$1,012,00 Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are \$0.00 reduced by 1/2. SUBTOTAL \$1,012.00 Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). 30 \$0.00 TOTAL NATIONAL FEE \$1,012.00 Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). \$0.00 TOTAL FEES ENCLOSED = \$1,012.00 Amount to be refunded S charged S A check in the amount of to cover the above fees is enclosed 07-1392 in the amount of _____\$1,012.00 _____ to cover the above fees. Please charge my Deposit Account No. b X A duplicate copy of this sheet is enclosed The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment IXI to Deposit Account No. 07-1392 A duplicate copy of this sheet is enclosed. Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card d information should not be included on this form. Provide credit card information and authorization on PTO-2038. NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status SEND ALL CORRESPONDENCE TO:

SEND ALL CORRESPONDENCE TO:

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REGISTRATION NUMBER

Page 2 of 2

April Zo 2001

JC02 Rec'd PCT/PTO 2. 0 APR 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Gordon J. DOW, et al

International Application No.:

PCT/GB99/03472

International Filing Date:

20 October 1999

Title: FLUTICASÓNE LOTION HAVING IMPROVED VASOCONSTRICTOR

ACTIVITY

Commissioner of Patents Washington, D.C. 20231

FIRST PRELIMINARY AMENDMENT

Dear Sir:

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information. Please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

In the Specification:

On the first line of the specification, after the Title, please add:

-- This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. PCT/GB99/03472 filed 20 October 1999, which claims priority from GB9823036.0 filed 22 October 1998 .--

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants haveamended the specification for purposes of adding the priority information. It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted;

James P. RIEK, 2, April 200

Attorney of Record, Reg. No. 39,009

GlaxoSmithKline

Corporate Intellectual Property Department

Five Moore Drive, PO Box 13398

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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

ABSTRACT

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

Via Facsimile

TO: PCT Examination International Bureau of WIPO 34 Chimin des Colombettes 1211 Geneva 20 Switzerland Fax: 011 41 22 740 1435	Correction to PCT Request before 30th Month
Applicant's File Reference	Applicant
PU3556WO	Glaxo Group Limited
International Application No.	International Filing Date:
PCT/GB99/03472	20 October 1999
30th Month Deadline: 22 April 2001	Title: Fluticasone Lotion Having Improved
	Vasoconstrictor Activity

Correction:

Please make the following correction to PCT Request PCT/GB99/03472 filed on 20 October 1999.

-Please change address of inventors/applicants: Keith Arthur JOHNSON; Frances Furr KELLY; Robert William LATHROP and Rukmini RAJAGOPALAN to:

GlaxoSmithKline c/o Corporate Intellectual Property Department Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709

Please acknowledge receipt of this request by return fax to (919) 483-7988 in the United States. If there should be questions, please call (919) 483-2252.

Thank you.

Christopher P. Rogers
Attorney for Applicant

PCT/GB99/03472

TO PROPER ROOM TO APPEAL OF

ELUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

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SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt.%, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14} - C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt.% of at least one skin conditioning agent; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt.%; a C14- C20 fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt.%; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt.%; at least one surfactant in an amount of about 0.25 to 3.0 wt.%; propylene glycol in an amount of from about 7.0 to 12.0 wt.%; up to about 10 wt.% mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroidresponsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the

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steps or acts of providing a lotion including about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a $\rm C_{14}\text{--}C_{20}$ fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt.% of one or more skin conditioning agents; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt.% preferably 0.005 to 0.5 wt.%, and more preferably about 0.005 to about 0.1 wt.%. The $\rm C_{1c} - \rm C_{20}$ fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The $\rm C_{1c} - \rm C_{20}$ fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt.%, preferably about 3.0 to 7.0 wt.%, and more preferably about 4.0 to 6.0 wt.%.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt.%, preferably about 1.0 to 3.0 wt.%, and more preferably about 1.0 to 2.0 wt.%. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about 5.0 wt.%, preferably about 0.5 to 3.0 wt.% and more preferably about 1.0 to 2.0 wt.% of the lotion composition.

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At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14} - C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt.%, preferably about 0.5 to 2.0 wt.%, and more preferably about 0.75 to 1.5 wt.%.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt.%. The lotion may also contain up to about 5.0 wt.% or up to about 2.0 wt.% skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt.%, preferably about 7.0 to 12.0 wt.% and more preferably 9.0 to 11.0 wt.%.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied

from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

91 -	invention was prepared named and removing	
20	Ingredient	(wt.%)
	Cetostearyl alcohol, NF	5.00
	Isopropyl myristate, NF	1.00
	Dimethicone 360, NF	1.00
	Cetomacrogol 1000, BP	1.00
25	Propylene glycol, USP	10.00
	Imidurea, NF	0.30
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Citric acid (anhydrous), USP	0.05
30	Sodium citrate, USP	80.0
	Purified water, USP	balance

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Example 2

A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	balance

Example 3

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	5.0
	Mineral Oil	3.0
25	Isopropyl myristate	3.0
	Ceteth-20	0.75
	Propylene Glycol	0.0
	Citric Acid (anhydrous)	0.05
	Dibasic Sodium Phosphate	0.06
30	Imidurea	0.20
	Water	balance

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Example 4

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(<u>wt.%)</u>
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.25
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phospha	te 0.06
Imidurea	0.20
Water	balance

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Example 6

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
25	Cetosteoryl Alcohol	7.0
	Isopropyl myristate	5.0
	Dimethicone	2.5
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
30	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
	Imidurea	0.30
	Water	balance

Example 8

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 9

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	4.7
25	Isopropyl myristate	3.75
	Dimethicone	3.75
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
30	Sodium Citrate	0.075
	Imidurea	0.30
	Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 11

	Ingredient	(wt.%)
	Fluticasone Propionate	0.01
25	Stearyl Alcohol	5.0
	Isopropyl myristate	3.0
	Dimethicone	3.0
	Ceteth-20	0.75
	Propylene Glycol	5.0
30	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	balance

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

	Ingredient	(wt.%)
25	Fluticasone Propionate	0.1
	Cetyl Alcohol	7.0
	Mineral Oil	2.0
	Isopropyl myristate	2.0
	Dimethicone	2.0
30	Cetomacrogol 1000	1.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
35	Water	balance

Example 14

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Aicohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 15

	Ingredient	(wt.%)
25	Fluticasone Propionate	0.1
	Cetostearyl Alcohol	5.0
	Mineral Oil	2.5
	Dimethicone	1.0
	Tween®40	0.5
30	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	balance

Example 16

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25
Mineral Oil	5.0
Brig®78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 17

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
	Cetyl Alcohol	2.0
25	Isopropyl myristate	5.0
	Cetomacrogol 1000	0.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
30	Propyl paraben, USP	0.10
	Water	balance

Example 18

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm² area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

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Table 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE® (Fluticasone proprionate) Cream
	- ZAMIPIO I		Comparative Example
AUC	C 28.4 26.7 21.4		21.4
Mean	1.58	1.49	1.22

^{*}Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

25 The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly

superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

Table 2

Treatment	Potency Responder Populat			opulation
		2 hour score	AUC	Avg. mean
				blanching
TEMOVATE™	High	2.7	36.6	2.0
ELOCON™	High	2.2	33.4	1.8
Fluticasone	Mid to High	2.1	26.7	1.5
lotion (0.05%)				
CUTIVATE™	Mid	1.8	21.4	1.2
Cream				
HYTONE™	Low	0.8	9.5	0.6
Lotion				

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

Ingradient

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005, FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

(set 0/s)

ingredient	(WL. 70)
fluticasone propionate (micronized)	0.05
cetostearyl alcohol, NF	5.0
isopropyl myristate, NF	1.0
dimethicone 360, NF	1.0
polyoxyethylene (20) cetostearyl ether, NF	1.0
propylene glycol, USP	10.0
imidurea, NF	0.14
methylparaben, NF	0.17
propylparaben, NF	0.06
citric acid (hydrous), USP	0.05
sodium citrate, USP	0.08
purified water, USP	balance (also QSAD)

Table 3

Study	Diagnosis	Application	No. subjects	Outcome
				Good to
				cleared(%)
FPL30003	Atopic	QD for up to	FPL (110)	FPL (78%)
	Dermatitis	4 weeks	Veh. (110)	Veh. (33%)
FPL30004	Atopic	QD for up to	FPL (111)	FPL (68%)
	Dermatitis	4 weeks	Veh. (107)	Veh. (28%)

^{*} subjects showing > 50% clearing of lesions

[&]quot;Veh." is vehicle only formulation

The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin (ACTH, 23) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

Table 4

Cortisol responses - plasma levels =18 ug/dL indicate suppression

Corticol respondes plasma	14.4.4	
Study	Preparation	Adrenal
		Responsiveness,
		#suppressed/total
FPL10005	Lotion	0 / 42

25 These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin (ACTH₁₋₂₈) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion.
30 These results were unexpectedly superior based on potency estimates from the VC Assav.

Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N=110 treated with fluticasone); FPL30004; N= 111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATE™ Cream and (2) that the side effects would reflect those observed for CUTIVATE™ Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

5 thereof:

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We claim:

- A topical lotion comprising: about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester
- about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt.% of at least one skin conditioning agent; about 5.0 to 15.0 wt.% propylene glycol; up to about 10.0 wt.% mineral oil or white soft paraffin; and the balance in water.
 - 2. A topical lotion comprising: about 0.005 to 1.0 wt. % fluticasone propionate; about 3.0 to 7.0 wt.% of a C₁₄-C₂₀ fatty alcohol, or mixtures thereof; about 0.5 to 3.0 wt.% of at least one skin conditioning agent; about 0.25 to 2.0 wt.% of at least one surfactant; about 7.0 to 12.0 wt.% propylene glycol; up to about 10 wt.% of mineral oil or white soft paraffin; and the balance in water.
 - 3. The lotion according to claim 1, further comprising less than about 5.0 wt.% dimethicone.
- 4. The lotion according to claim 2, further comprising less than about 5.0 wt.% 25 dimethicone.
 - The lotion according to claim 1, wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.
- 30 6. The lotion according to claim 1, comprising: about 0.05 wt.% fluticasone propionate, about 5.0 wt.% cetostearyl alcohol, about 1.0 wt.% isopropyl myristate, about 1.0 wt.% dimethicone,
- 35 about 1.0 wt.% cetomacrogol,

about 10.0 wt.% propylene glycol less than about 0.30 wt.% imidurea, less than about 0.20 wt.% methyl paraben, less than about 0.10 wt.% propyl paraben, about 0.05 wt.% citric acid (anhydrous), about 0.08 wt.% sodium citrate, and the balance in purified water.

- 7. The lotion according to claim 1, comprising: about 0.05 wt.% fluticasone propionate, about 5.25 wt.% cetostearyl alcohol, about 2.0 wt.% isopropyl myristate, about 10.0 wt.% propylene glycol, about 0.20 wt.% imidurea, about 0.20 wt.% methyl paraben, about 0.10 wt.% propyl paraben, and the balance in purified water.
- The lotion according to claim 1, having a viscosity of about 2,000 to 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.
- The lotion according to claim 2, having the formula about 5.25 wt.% cetostearyl alcohol, about 2.0 wt.% isopropyl myristate,
 about 10.0 wt.% propylene glycol, about 0.20 wt.% imidurea, about 0.20 wt.% methyl paraben, about 0.10 wt.% propyl paraben, and the balance in purified water.

10. The lotion according to claim 1, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

- 11. The lotion according to claim 2, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.
- 5 12. The lotion according to claim 1, free of mineral oil or white soft paraffin.
 - 13. The lotion according to claim 2, free of mineral oil or white soft paraffin.
 - 14. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.
 - 15. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone proprionate.
 - 16. A process for preparing a lotion according to claim 1, comprising: mixing the ingredients recited in claim 1 at an elevated temperature; and cooling said mixture.
 - 17. A process for preparing a lotion according to claim 1, comprising: mixing the ingredients recited in claim 1 at an elevated temperature; and heating said mixture.
 - 18. A topical lotion comprising:

the balance in water.

- about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
 - a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; an emulsifying effective amount of a surfactant, and
 - 19. The lotion of claim 18, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

- 20. The lotion of claim 18, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.
- 21. A method of treating a skin condition comprising: providing a lotion including about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof, about 1.0 to about 10.0 wt.% of a least one skin conditioning agents; about 5.0 to about 15.0 wt.% of at least one skin conditioning agents; about 5.0 to about 15.0 wt.% of propylene glycol; less than about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in water; and, applying the lotion to the skin having the skin condition.
- 22. The method of claim 21, wherein the skin condition is corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting or pruritis.
- 23. The topical lotion of claim 21, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.
- 24. The lotion of claim 21, wherein the lotion is chemically and physically stable for at least 6 months at 40° C.

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COMBINED DECLARATION FOR UTILITY OF DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

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0 1 2	OF INVENTOR'S INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP ' POST OFFICE ADDRESS FULL NAME OF INVENTOR INVENTOR'S SIGNATURE RESIDENCE &	DOW CITY Petaluma POST OFFICE ADDRESS Dow Pharmaceutical Scie 1330A Redwoodway FAMILY NAGE JOHNSON CITY Durham POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 133	STATE OR FORE CA CITY Petaluma FIRST GIVEN Keith STATE OR FORE NC CITY Research	NAME GR COUNTRY Triangle Park	J. COUNTRY OF CITIZE US STATE & ZIP CODEC: CA 94954, US SECOND GIVEN NAM Arthur COUNTRY OF CITIZE US STATE & ZIP CODEC: NC 27709, US	NSHIP OUNTRY E-INITIAL NSHIP OUNTRY
0 1 2 0	OF INVENTOR: SIGNATURE RESIDENCE & CITIZENSHIP POSTORICE ADDRESS PULL NAME OF INVENTOR: SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR INVENTOR: INVENTOR: INVENTOR: INVENTOR: INVENTOR	DOW CITY Petaluma POST OFFICE ADDRESS DOW Pharmaceutical Scie 1330A Redwoodway FAMILY NAME JOHNSON CITY Durham POST OFFICE ADDRESS GlaxOSmithKline Five Moore Drive, PO Box 133 FAMILY NAME KELLY	Gordon STATE OR FO CA CITY ence Petaluma FIRST GIVEN Keith STATE OR FOREI NC CITY Research	NAME GR COUNTRY Triangle Park	COUNTRY OF CITIZE US STATE A ZE CORDEC CA 94954, US SECOND GIVEN NAMI ATTHUT COUNTRY OF CITIZE US STATE A ZE CORDEC NC 27709, US SECOND GIVEN NAMI	NSHIP OUNTRY E-INITIAL NSHIP OUNTRY
0 1 2 0 2	OF INVENTOR: SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S SIGNATURE RESIDENCE & CITIZENSHIP POST OFFICE ADDRESS FULL NAME OF INVENTOR'S FULL NAME OF INVENTOR'S FULL NAME OF INVENTOR OFFICE OF INVENTOR	DOW CITY Petaluma POST OFFICE ADDRESS DOW Pharmaceutical Scie 1330A Redwoodway FAMILY NAME LOTY Durham POST OFFICE ADDRESS CJACK OFFIC	GOPDON STATE OR FOR CA CITY Petaluma FIRST GIVEN Keith STATE OR FORE NC CITY Research FIRST GIVEN NA	NAME Triangle Park 48	COUNTRY OF CITIZE US STATE A ZE CORDEC CA 94954, US SECOND GIVEN NAMI ATTHUT COUNTRY OF CITIZE US STATE A ZE CORDEC NC 27709, US SECOND GIVEN NAMI	NSHIP SSHIP OUNTRY SSHIP OUNTRY EMITIAL 8 200/ NSHIP

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	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEYS BOCKET NUMBER PU3556USW							
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued							
(t)	FULL NAME OF INVENTOR	LATHROP	Robert	SECOND GIVEN NAME/INITIAL William				
fci	INVENTOR'S SIGNATURE	* Lattery	Robert	COUNTRY OF CITIZENSHIP				
0	RESIDENCE & CITIZENSHIP	Fort Collins	CO STATE OF FOREIGN COUNTRY	US STATE & ZIP CODE/COUNTRY				
4	POST OFFICE ADDRESS	FOST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US				
2	FULL NAME OF INVENTOR	RAJAGOPALAN	FIRST GIVEN NAME Rukmini	SECOND GIVEN NAME/INITIAL				
	INVENTOR'S SIGNATURE		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP				
°	RESIDENCE & CITIZENSHIP	Durham	NC CITY	US STATE & ZIP CODE/COUNTRY				
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US				

DECLARATION FOR "371" APPLICATION

COM	COMBINED DECLARATION FOR UTILITY or DESIGN ATTRIBUTE SOURCE PU3556USW ATTRIBUTE SOURCE PU3556USW							
PAT	ENT APPLI	CATION WITH POWE	ER OF ATTORNEY Con	ntinued				
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL				
2	OF INVENTOR	LATHROP	Robert	William				
1	INVENTOR'S							
	SIGNATURE			COUNTRY OF CITIZENSHIP				
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	US				
ì	CITIZENSHIP	Fort Collins	CO	STATE & ZIP CODE/COUNTRY				
į .	POST OFFICE	POST OFFICE ADDRESS	Research Triangle Park	NC 27709, US				
4	ADDRESS	GlaxoSmithKline	Research Thangle Lark	110 21705, 05				
		Five Moore Drive, PO Box 13398		SECOND GIVEN NAME/INITIAL				
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME Rukmini	SECOND GEVEN HADISH GIVE				
(2)	OF INVENTOR	RAJAGOPALAN	A CONTRACTOR OF THE PARTY OF TH					
56E)	INVENTOR'S	Kajagopalan		(10APR2001				
1	SIGNATURE		-	COUNTRY OF CITIZENSHIP				
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	US				
i	CITIZENSHIP	Durham	NC /V	STATE & ZIP CODE/COUNTRY				
1	POST OFFICE	POST OFFICE ADDRESS	CITY	NC 27709. US				
5	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, 03				
1		Five Moore Drive, PO Box 13398						

DECLARATION FOR "371" APPLICATION ATTORNEY'S DOCKET COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT PU3556USW APPLICATION WITH POWER OF ATTORNEY First Names Inventor: Gordon J. DOW Complete if known: App No.: (X) Declaration submitted with initial filing or ()Declaration submitted after initial filing (surcharge required 37CFR1.16(e)) Filing Date Group Art Unit: As below named inventor. I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: 500 FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY the specification of which (check only one item below): CCUY OFFICE []is attached hereto. [x] was filed on 20 October 1999 as United States application Serial No. or PCT International Application Number PCT/GB99/03472 filed and was amended on (MM/DD/YYYY) applicable) I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

DRIOD EODEICN AND ANY PRIODITY CLAIMS UNDER 35 U.S.C. 110

Prior Foreign Application	Country	Foreign Filing Date	PRIORITY
Number (s)		(MM/DD/YYYY))	CLAIMED
1. 9823036.0	GB	22 October 1998	X
2.			
3.			
4.			
5.			

Applic	ation No.	Filing Date (MM/DD/YYYY)		
1.				
2.				
3.				
4.				
5.				

	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEYS DOCKET NUMBER PU3556USW							
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued							
2	FULL NAME OF INVENTOR	LATHROP						
	INVENTOR'S SIGNATURE	City	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP				
0	RESIDENCE & CITIZENSHIP	Fort Collins	СО	US				
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US				
2	FULL NAME OF INVENTOR	FAMILY NAME RAJAGOPALAN	FIRST GIVEN NAME Rukmini	SECOND GIVEN NAME/INITIAL				
	INVENTOR'S SIGNATURE							
0	CITIZENSHIP Durham NC US							
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US				

		DECLAR	RATION FOR "371"	APPLICATION	
	IBINED DECLAR LICATION WITH			OR DESIGN PATENT EY	ATTORNEY'S DOCKET PU3556USW Fust Names Inventor: Gordon J. DOW
					Complete if known:
(X) Dec	laration submitted with initial	App No.:			
()Decl	aration submitted after initial	filing (surcharge rec	quired 37CFR1.16(e))		Filing Date
					Group Art Unit:
	As below named	d inventor. I herel	by declare that:		
	My residence, post office	address and citiz	enship are as stated	below next to my name.	
	I believe I am the origina (if plural names are listed entitled:	l, first and sole in I below) of the sul	ventor (if only one i	name is listed below) or an original, s claimed and for which a patent is s	first and joint inventor sought on the invention
	FLUTICA the specification of which			OVED VASOCONSTRICTOR AC	CTIVITY
	[]is attached hereto. OR				
LI N				on Serial No or PC	
t Fall	Application Number PC applicable)	T/GB99/03472 fi	led_and was amende	ed on (MM/DD/YYYY)	(if
	as amended by any amen	ndment specificall	y referred to above.	s of the above-identified specification	
ļa:	I acknowledge the duty t	o disclose informa	ation which is mater	rial to patentability as defined in 37	CFR §1.56.
	or inventor's certificate of United States of America patent or inventor's certification which priority is claimed	or 365(a) of any Po a, listed below and ficate or of any Po d:	CT international app I have also identified CT international app	(a)-(d) or §365(b) of any fereign ap dication which designated at least of d below, by checking the box, any f lication having a filing date before	ne country other than the oreign application for
	R FOREIGN AND ANY I				PRIORITY
	or Foreign Application Number (s)		Country	Foreign Filing Date (MM/DD/YYYY))	CLAIMED
	3036.0		GB	22 October 1998	X
2.					
4.					
5.					
I hereb		Title 35, United St		of any United States provisional app	lication(s) listed below:
1.	Application No.		riling	Date (MM/DD/YYYY)	
2.	4,000				

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		CLARATION FOR U		PU3556USW
PAT	ENT APPLI	CATION WITH POW	ER OF ATTORNEY	Continued
2	FULL NAME OF INVENTOR	FAMILY NAME LATHROP	Robert	SECOND GIVEN NAME/INITIAL William
	INVENTOR'S SIGNATURE	CHY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
0	RESIDENCE & CITIZENSHIP POST OFFICE	Fort Collins	CO	US STATE & ZIP CODE/COUNTRY
4	ADDRESS	GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US
2	FULL NAME OF INVENTOR	FAMILY NAME RAJAGOPALAN	FIRST GIVEN NAME Rukmini	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
0	RESIDENCE & CITIZENSHIP	Durham POST OFFICE ADDRESS	NC	US STATE & ZIP CODE/COUNTRY
5	POST OFFICE ADDRESS	GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US

		DECLARATI	ON FOR 3/1 A	PPLICATION		
APPI	BINED DECLAR LICATION WITH	POWER OF		R DESIGN PATENT	PU355 First Nan Gordon	nes Inventor: n J. DOW ete if known:
			1.22CPD 1.16(-))		1	1
()Decl	aration submitted after initial f	iling (surcharge required	13/CFR1.16(e))		Filing I	Date
					1	Juic
					Group .	Art Unit:
	As below named	inventor. I hereby de	clare that:			
	My residence, post office	address and citizensh	ip are as stated belo	ow next to my name.		
				e is listed below) or an original, aimed and for which a patent is		
54 60 64	FLUTICA the specification of which			ED VASOCONSTRICTOR A	CTIVITY	l
L)	[]is attached hereto. OR					
Xi.	[x] was filed on 20 Octo	ober 1999 as United S	States application S	Serial No or Po	CT Interna	tional
DHEG	Application Number PC applicable)	Γ/GB99/03472 filed a	nd was amended o	on (MM/DD/YYYY)		_(if
	I hereby state that I have as amended by any amended			the above-identified specification	on, includi	ng the claims,
	I acknowledge the duty to	disclose information	which is material	to patentability as defined in 37	CFR §1.56	5.
	or inventor's certificate or	365(a) of any PCT ir	ternational applica	-(d) or §365(b) of any foreign a stion which designated at least of slow, by checking the box, any f	ne country	other than the
	patent or inventor's certifi- which priority is claimed:		ternational applica	tion having a filing date before	that of the	application on
PRIOF	FOREIGN AND ANY P	RIORITY CLAIMS	UNDER 35 U.S.C	C. 119:		
Prio	r Foreign Application Number (s)	Count	ту	Foreign Filing Date (MM/DD/YYYY))		PRIORITY CLAIMED
1. 982.	3036.0	GB		22 October 1998		X
2.						
3.						
4.						
5.	1: 1 : 7: 7: 7: 7: 7: 7: 7: 7: 7: 7: 7: 7: 7	11 25 TV 11 1 2 1 1 1 1				
1 nereb		itie 33, United States		y United States provisional app	lication(s)	nsted below:
1.	Application No.		Filing Date	e (MM/DD/YYYY)		
2.					-	
3.						
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CON	MBINED DE	CLARATION FOR U	TILITY or DESIGN		ATTORNEY'S DOCKET NUMBER PU3556USW
PAT	ENT APPLI	CATION WITH POW	ER OF ATTORNEY	Continued	
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME		D GIVEN NAME/INITIAL
2	OF INVENTOR	LATHROP	Robert	Willi	am
	INVENTOR'S				
	SIGNATURE				
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY		RY OF CITIZENSHIP
	CITIZENSHIP	Fort Collins	CO	US	
	POST OFFICE	POST OFFICE ADDRESS	CITY		& ZIP CODE/COUNTRY
4	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 2	7709, US
	l	Five Moore Drive, PO Box 13398			
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECON	D GIVEN NAME/INITIAL
2	OF INVENTOR	RAJAGOPALAN	Rukmini		
	INVENTOR'S				
	SIGNATURE	1		1	
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY		RY OF CITIZENSHIP
	CITIZENSHIP	Durham	NC	US	
	POST OFFICE	POST OFFICE ADDRESS	CITY		& ZIP CODE/COUNTRY
5	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 2	7709, US
)	Five Moore Drive, PO Box 13398	1		

				DESIGN PATENT	PU3556	EY'S DOCKET USW
APPI	ICATION WITH	POWER C	F ATTORNEY		First Name	es Inventor.
					Gordon	J. DOW
					Complet	e if known:
(X) Dec	laration submitted with initial	filing or			App No.	:
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()Decia	aration submitted after initial fi	nng (surcharge rec	julied 3/CFK1.10(e))		Filing D	ate
					Group A	nd T Touit
					Group A	at omt.
	As below named	inventor. I herel	by declare that:			
	My residence, post office	address and citiz	enship are as stated belo	w next to my name.		
	I believe I am the original	, first and sole in	ventor (if only one name	e is listed below) or an original,	first and jo	int inventor
C)	(if plural names are listed entitled:	below) of the sul	bject matter which is cla	imed and for which a patent is so	ought on ti	he invention
Q	FLUTICA	SONE LOTION	HAVING IMPROVE	D VASOCONSTRICTOR AC	TIVITY	
300	the specification of which					
	[]is attached hereto. OR					
1	[x] was filed on 20 Octo	ber 1999 as Un	ited States application S	erial No or PC	T Internat	ional
	Application Number PC: applicable)	Г/ GB99/03472 fi	iled_and was amended or	n (MM/DD/YYYY)		_(if
	I hereby state that I have a as amended by any amend	eviewed and und Iment specificall	derstand the contents of y referred to above.	the above-identified specification	n, includin	g the claims,
lant lank				o patentability as defined in 37 (CFR §1.56	.
	I hereby claim foreign pri	ority benefits un	der 35, U.S.C. §119 (a)-	(d) or §365(b) of any foreign ap	plications(s) for patent
l	or inventor's certificate or	365(a) of any P	CT international applica	tion which designated at least or	ne country	other than the
1	United States of America	, listed below and	l have also identified be	low, by checking the box, any for tion having a filing date before the	oreign app	lication for
1	which priority is claimed:		_1 international applicat	non naving a ming date before t	nat or the a	ipplication on
	R FOREIGN AND ANY P			. 119: Foreign Filing Date		PRIORITY
Pric	or Foreign Application Number (s)	(Country	(MM/DD/YYYY))		CLAIMED
1. 982	3036.0		GB	22 October 1998		X
2.						
3.						
4.						
5.						
I hereb	y claim the benefit under T	itle 35, United S		y United States provisional appl	ication(s)	listed below:
	Application No.		Filing Date	(MM/DD/YYYY)		
1.						
2.						
3.			l			

COMBINED DECLARATION FOR UTILITY OF DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEYS DOCKET NUMBER
PU3556USW

I hereby claim the benefit under 35, U.S.C. § 120 of any United States application or § 3265(e) of any PCT international designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosured in the proof United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 11.2, I acknowledge the duty to disclose information which is material to patentiability as defined in 37 C.F.R. § 1.56 which became available between the filling date of the prior application(s) and the national or PCT international filling date of this application:

UOR	U.S. PARENT A	PPLICATION or I	CITAKENTALL	LICAIL		STATUS (Check	one)
U.S.	Parent Application or	PCT Parent	Parent Filing Date		PATENTED	PENDING	ABANDONED
	Number		(MM/DD/YYYY))			
						_i	
WER	OF ATTORNEY: A	s a named inventor, I her	eby appoint the following	g attorney(s)	and/or agent(s) to pro	secute this application	and transact all busines
U.S. 1	Patent and Trademark	Office connected therewi	th. (List name and regist	ration numb	er)		
		Reg. No. 27,655	James P. Ri	ale	Reg. No. 39,009	Bonnie L. Depnenb	rock Reg. No. 28,209
D23	rid J. Levy arles E. Dadswell	Reg. No. 27,055 Reg. No. 35,851	Virginia C.		Reg. No. 37,092		z Keg. No. 37,386
t Vo	an I Drue	Reg. No. 39,337	Frank P.Gra		Reg. No. 31,164		
Rol	pert H. Brink	eg. No. 36,094	Christopher		Reg. No. 36,334		
	abeth Selby	Reg. No. 38,298	Lorie Ann l	Morgan	Reg. No. 38,181		
1						T	
nd C	orrespondence to:		1,99001007	11 (411 (414 (114))	19/90	Direct Telephone C	ans (0)
	David J. Levy, Pat	ent Counsel	1444		MM	Christo	pher P. Rogers
J		Property Department		3347			-483-1240
Ų.	Glaxo Wellcome In		_				
14	Five Moore Drive, Research Triangle	PU Box 13398	PATENT	TEAT.EMARK	OFFICE		
1	Research Triangle	Fark, NC 27709					
3	and belief are be	elieved to be true; an the like so made are p tements may jeopard	d further that these s punishable by fine o ize the validity of th	statements r imprisor le applicat	were made with t ment, or both, un ion or any patent	the knowledge that der 18 U.S.C. 1001 issuing thereon.	, and that such
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2	and belief are be statements and willful false state	elieved to be true; an the fike so made are tements may jeopard	d further that these s punishable by fine o ize the validity of th	statements or imprisor ie applicat st given nar	were made with t ment, or both, un ion or any patent	the knowledge that der 18 U.S.C. 1001 issuing thereon.	, and that such
	and belief are be statements and willful false state FULL NAME OF INVENTOR	elieved to be true; and the fike so made are tements may jeopard DOW	d further that these spunishable by fine of ize the validity of the	statements or imprisor ne applicat st given nar ordon	were made with timent, or both, union or any patent	der 18 U.S.C. 1001 issuing thereon. SECOND GIVEN NAS J.	, and that such
3	and belief are be statements and willful false statements and willful false statements of inventors inventors signature residence &	elieved to be true; and the fike so made are tements may jeopard DOW	d further that these s punishable by fine o ize the validity of th	statements in imprisor ie applicat st given nar ordon	were made with t ment, or both, un ion or any patent	der 18 U.S.C. 1001 issuing thereon. SECOND GIVEN NAM J. COUNTRY OF CITIZ	, and that such
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DECLARATION FOR "371" APPLICATION COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT ATTORNEY'S DOCKET PU3556USW APPLICATION WITH POWER OF ATTORNEY First Names Inventor: Gordon J. DOW Complete if known: App No.: (X) Declaration submitted with initial filing or ()Declaration submitted after initial filing (surcharge required 37CFR1.16(e)) Filing Date Group Art Unit: As below named inventor. I hereby declare that: My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY the specification of which (check only one item below): []is attached hereto. [x] was filed on 20 October 1999 as United States application Serial No. ______ or PCT International Application Number PCT/GB99/03472 filed and was amended on (MM/DD/YYYY) applicable) I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56. I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed: PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119: PRIORITY Foreign Filing Date Country Prior Foreign Application CLAIMED (MM/DD/YYYY)) Number (s) 22 October 1998 1. 9823036.0 4. I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	

COMBINED DECLARATION FOR UTILITY OF DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER
PU3556USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to paternability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or

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